STATS 275 Individual Project

# Analysis of Effect of Mother's Stress in the Estimated Fetal Weight

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**Abstract**

**Background** Stress is a unavoidable factor in our life. People usually thinks that stress leads to changes in a pregnant woman's body. The level of stress hormones may increase, for example, affecting fetal development. However, the precise mechanism of how stress affects the baby in the womb is not yet been completely clarified. There is an immense interest in how stress level would affect the growth of fetal. Our study focus on the relationship between the Estimated Fetal Weight and mother's stress level during pregnancy.

**Method** I used linear regression model by R software to analyze the collected data of 100 patients with response variable, EFW, and the primary variable of interest, Scort. The Wald statistics was used to test the significance of the association of last measurement of EFW and Scort given all other confounding variables in the model and the association of change of EFW and change of Scort based on first and last measurements.

To access the relationship between EFW and Scort change over the course of GA, I applied a main linear mixed effect model. A Likelihood ratio was conducted to test whether the relationship between EFW and Scort change over GA.

**Results** There is no significant association between EFW and Scort focusing on the last measurement.(P value=0.54). Moreover, focusing on the first and last measurements of EFW and Scort for each subject, the change in cortisol is not related to the change in EFW.(P value=0.89). Finally, there is lack of enough statistical evidence to support that the relationship between EFW and Scort change over the GA, using all available longitudinal measurements..(P value=0.58). In conclusion, we could not find enough statistical evidence that there is relationship between Estimated Fetal Weight though this study.

## 1 Introduction

Stress[1] is a feeling of emotional or physical tension. It can come your body's reaction to a challenge or demand. In short bursts, stress can be positive, such as when it helps you avoid danger or meet a deadline. But when stress lasts for a long time, it may harm your health.

There are some previous researches[1][2] documenting that high levels of stress that continue for a long time may cause health problems, like high blood pressure and heart disease. In particularwomen who exhibit elevated high levels of stress symptoms during pregnancy are at increased risk for delivering premature(born before 37 weeks of pregnancy) and low birthweight infants(weighing less than 5 pounds).

However, the precise mechanism of how stress affects the baby in the womb is not yet been completely clarified. In cooperation with the University Hospital Zurich and the Max Planck Institute Munich, researchers of the University of Zurich[3] have discovered that physical stress to the mother can change the metabolism in the placenta and influence the growth of the unborn child. They found that short-term stress would no affect on the growth of the fetus Meanwhile, if the mother is stressed for a longer period of time, the CRH level in the amniotic fluid increases. This higher concentration of stress hormone in turn accelerates the growth of the fetus.

Therefore, it would be our interest to explore the relationship between EFW and mother's stress level during pregnancy .

# 2 Methods

## 2.1 Data Collection

The data was collected longitudinally over gestational age(GA in weeks) on 100 patients. The response variable is Estimated Fetal Weight(EFW in grams), and the primary variable of interest is salivary cortisol (Scort in $\mu$g/dL)which is used as a stress index. Besides EFW and Scort, some other variables[4], mother's Boday Mass Index(BMI) before pregnancy, child's gender, mother's race, and the presence of major medical complications during pregnancy that were identified as potenial confounding factors in previous study have been recorded. Since Race is a nominal variable that we need to factorize it first.

There are 100 unique patients, each patient was recorded for five measurements with response variable, EFW, the primary variable, Scort and the time variable, GA. All patients have the completed records. Therefore data analysis is conducted as a complete fashion.

## 2.2 Scientific Goals

This study mainly focus on the following three Goals:

- Examine the association between EFW and Scort focusing on the last measurement(ObsNum=5) .
- Conduct an appropriate analysis to assess the relationship between the change in EFW and the change in cortisol during prenancy given first(ObsNum=1) and last measurements(ObsNum=5) of EFW and Scort for each subject.
- Using all available longitudinal measurements during pregnancy, examine the relationship between EFW and Scort change over the course of GA.

## 2.3 Statistical Methods

To address the first question, a linear regression model(Model 1) was chosen to explore the association between EFW and Scort based on the last measurement (ObsNum=5). According to the previous researches, BMI, child's gender, mother's race, obstetric risk would affect the estimated fetal weight. Meanwhile, there is no doubt that the older gestational age is associated with larger estimated fetal weight. Hence, the variables mentioned before should be addressed in the model. Note that each individual only has one value representing the EFW and Scort of last measurement. Hence there won't be within subject variation. Therefore, we chose a simple linear regression for simplicity and we applied robust variation estimator to obtain a standard errors.

$EFW_i$ and $Scort_i$ represent the EFW and salivary cortisol of patient i at the last measurement.

$$\begin{aligned} EFW_i =& \beta_0 + \beta_1 GA_i + \beta_2 Scort_i + \beta_3 BMI_i + \beta_4 Igender_i + \beta_5 IriskOB_i + \\ & \beta_6 Irace_{AfricanAmerican} i + \beta_7 Irace_{Others} i + \epsilon_i \end{aligned} \tag{1}$$

Where $gender_i$=1 represents the child's gender is male, $riskOB_i$=1 defined as the presence of major medical complications during pregnancy of patient i, $race_{AfricanAmerican}$=1 represents the patient i is African American, $race_{Others}$=1 represents the patient i is other race besides White and African American.

In order to test the hypothesis that whether Scort has an effect on EFW based on the last measurement. Test for significance of association was conducted with the Wald test. The null hypotheses is $H_0$ $\beta_{Scort} = 0$, the alternative is there is a significant association between EFW and Scort. The significance level the test was taken to be 0.05. Further, we checked the residual to determine whether the variance assumption is reasonable and a Q-Q plot was drawn to check the normality assumption.

As for the second scientific goal, focusing on the first(ObsNum=1) and last(ObsNum=5) measurements of EFW and Scort for each subject, how is the change in cortisol related to the change in EFW during pregnancy. Firstly, we compute the change in EFW and cortisol by subtracting the individual record of last measurement and first measurement. Since the confounding variables BMI, child's gender, mother's race, obstetric risk and time variable gestational age would affect the change of EFW, we would address these variables in the model.

$EFWd_i$, $Scortd_i$ and $GAd_i$ represent the change in EFW, salivary cortisol and gestational age of patient i between the first and last measurement.

the model is

$$
\begin{aligned}
EFWd_i = &\beta_0 + \beta_1 GAd_i + \beta_2 Scortd_i + \beta_3 BMI_i + \beta_4 Igender_i + \beta_5 IriskOB_i + \\
&\beta_6 Irace_{AfricanAmerican} i + \beta_7 Irace_{Others} i + \epsilon_i
\end{aligned}
\tag{2}
$$

To assess the hypothesis that whether the change in cortisol is related to the change in EFW focusing on the first and last measurements. Similar to first goal, the Wald test was conducted. The null hypotheses is $H_0$ $\beta_{Scortd} = 0$, the alternative is the change in cortiol is significantly related to the change in EFW. The significance level the test was taken to be 0.05.

As for the last scientific goal, a main effect linear mixed effect model was built to investigate the relationship between EFW and Scort change over the course of GA using all available longitudinal measurements. The linear mixed effect model allows for individual variation in the intercept. And one of the pros of likelihood based methods is that we can utilize likelihood ratio test to determine whether there is association between EFW and Scort change over the course of GA. The model is fitted with maximum likelihood method because we will not be able to conduct likelihood ratio test if we fitted with REML. To address the scientific goal, we add an interaction term between Scort and GA to access whether the relationship between EFW and Scort would change across the GA.

Notice that[5]mentioned,the average singleton fetus weighs about 80 grams by the end of the first trimester and grows increasingly faster after 22 weeks to reach a maximum growth rate of almost 220 grams per week by 35 weeks. Growth then slows down and is about 185 grams per week by 40 weeks. The article implied that the relationship between EFW and GA may not be linear which we need explore further in exploratory data analysis.

# 3 Result

## 3.1 Exploratory Data Analysis

In this part we perform a preliminary descriptive data analysis to explore the data set and provide evidence of how Scort may affect the growth up of EFW at last measurements, how the change in Scort might influence on the change in EFW during pregnancy, and how the relationship between EFW and Scort change over the course of GA.

To begin with, the histogram of continuous variables(EFW,Scort,GA,BMI) in the last measurements was drawn to understand how it is distributed. As it can be observed from figure 1(in Appendix ), they are approximately normally distributed. The next step was to look at the correlation matrix, it suggests that gestational age is highly positive correlated to EFW, the older gestational age the heavier estimated fetal weight which is consistent with the common sense, therefore, GA might be a better predictor than Scort.

Furthermore, it's interesting that we could not find any pattern between EFW and Scort from the figure 3.

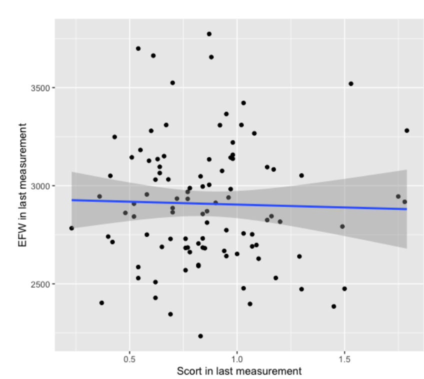


Figure 1: Explore the relationship between EFW and Scort based on the last measurement

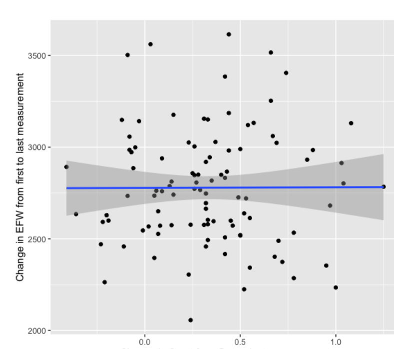


Figure 2: Explore the relationship between the change of EFW and Scort based on the first and last measurement

Also, we notice from figure 4,5,6(in Appendix), there are only slightly difference of the estimated fetal weight between child's gender, mother's race and having major medical complication during pregnancy or not.

Moreover,in order to explore the association between the change in EFW and the change in Scort based on the first and last measurements, we create a ggplot(figure ) in R, it is shown that there is no evident pattern between the change of EFW and the change of Scort.

In order to explore the the relationship between EFW and Scort change over the course of GA, since EFW, GA and Scort are continuous variable then it is hard to represent their relationship on the plot. Meanwhile, since GA and the measurements are highly correlated. The first measurement of patients are among 15-19 gestation age, the second measurement of patients are among 19-24 gestation age, the third measurement of patients are among 23-30 gestation age, the fourth measurement of patients are among 29-35 gestation age, the last measurement of patients are among 35-40 gestation age. Here, we class GA into 5 category which represented by 5 measurement time. A scatter plot of different measurement time of EFW over Scort was plot.

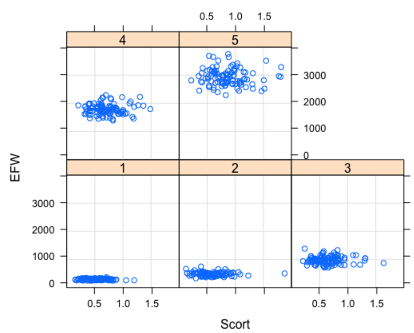


Figure 3: Explore the relationship between EFW and Scort categorized by measurement time

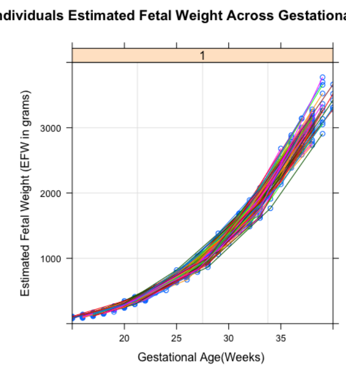


Figure 4: Explore the trajectory of the individual change of EFW across the GA

As shown in Figure , it appears that there is no pattern between EFW and Scort in different measurement times. The value of EFW increased as GA increased while the value of Scort inflates among 0-1.5 during the pregnancy.

Since we suspect the relationship among EFW and GA may not be linear,spaghetti plots of EFW over GA were made. Each line represents the change of EFW over GA of a particular individual. As shown in Figure above, we found find that the relationship between EFW and GA are not linear obviously, the increase of EFW tend to be quadratic trend as GA increased. We need to consider whether should we put quadratic term of GA in our model inference.

## 3.2 Model Inference

**Modeling last measurement of EFW and Scort** To analyze the association between EFW and Scort for each subject, focusing on the last measurement, a simple linear regression was constructed adjusting for all other confounding variable. The result of simple linear regression model is provided in table :

| | Estimate | Robust SE | ci95.lo | ci95.hi | t value | Pr(>\|t\|) |
|---|---|---|---|---|---|---|
| (Intercept) | -4671.89 | 468.13 | -5601.63 | -3742.15 | -9.98 | 0.00 |
| GA | 203.54 | 13.50 | 176.72 | 230.36 | 15.07 | 0.00 |
| Scort | -33.67 | 54.26 | -141.44 | 74.10 | -0.62 | 0.54 |
| BMI | 2.30 | 2.70 | -3.06 | 7.65 | 0.85 | 0.40 |
| Gender | -25.77 | 32.99 | -91.30 | 39.75 | -0.78 | 0.44 |
| RiskOB | -35.62 | 37.24 | -109.59 | 38.34 | -0.96 | 0.34 |
| Race2 | -19.02 | 40.70 | -99.85 | 61.82 | -0.47 | 0.64 |
| Race3 | -39.24 | 33.46 | -105.70 | 27.21 | -1.17 | 0.24 |

Table 1: Result of model 1

As we can observe from table, 1 $\mu$g/dL increased in salivary cortisol is associated with 33.67 grams decreased in the mean of estimated fetal weight with all other variables held constant.(95% CI(-141.44,74.1)grams)

We construct a Wald test to test the association between EFW and Scort. The null hypothesis is there is no association between EFW and Scort($\beta_S cort = 0$). The result of the test statistic is -0.62 with p-value 0.54. For the population of patients there is lack of statistically significant evidence to support that Scort is associated with a lower Estimated Fetal Weight.

Model diagnostics are performed and from the residual plot and QQ plot (in Appendix), we observe that the residuals are approximately normally distributed around 0. No outlier is found in this process.

**Hypothesis about change in cortisol related to the change in EFW** As the previous model shows that there is no significant association between EFW and scort, focusing on the last measurement. We would be curious about how is the change in salivary cortisol related to the change in EFW, focusing on the first and last individual measurements. The analysis was fairly straight-forward, a simple linear regression was implemented.

| | Estimate | Robust SE | ci95.lo | ci95.hi | t value | Pr(>\|t\|) |
|---|---|---|---|---|---|---|
| (Intercept) | -331.13 | 242.71 | -813.17 | 150.90 | -1.36 | 0.18 |
| BMI | 5.08 | 3.47 | -1.82 | 11.97 | 1.46 | 0.15 |
| Gender | 53.63 | 44.60 | -34.94 | 142.20 | 1.20 | 0.23 |
| RiskOB | -45.61 | 45.03 | -135.05 | 43.83 | -1.01 | 0.31 |
| Race2 | -23.70 | 60.27 | -143.40 | 96.00 | -0.39 | 0.70 |
| Race3 | -147.83 | 45.48 | -238.16 | -57.50 | -3.25 | 0.00 |
| GAd | 144.69 | 13.38 | 118.12 | 171.27 | 10.81 | 0.00 |
| Scortd | 9.38 | 66.37 | -122.44 | 141.19 | 0.14 | 0.89 |

Table 2: Result of model 2

From the table 2, we found that the 1 $\mu$g/dL increased in the change of salivary cortisol is associated with 9.38 grams increased in the mean change of estimated fetal weight with all other variables held constant.(95% CI(-122.44,141.39) grams)

Considering hypothesis that the association between the change in cortisol and change in EFW, we test the significance of this effect using the Wald test. The null hypothesis is the change in cortisol is no related to the change in EFW during pregnancy. The result of the test statistic is 0.14 with p-value 0.89. We could not reject the null hypothesis, there is not enough statistical evidence to show that the change in cortisol is related to the change in EFW during pregnancy in the population level.

**Explore the relationship between EFW and Scort change over the GA** In this part, we built a linear mixed effect model (Model 3) with interaction term of Scort and GA, and random intercept in order to characterize the relationship between EFW and Scort change over the course of GA using all available longitudinal measurements during pregnancy. The model we that first considered was :

$$\begin{aligned} EFW_{ij} =& \beta_0 + \beta_1 GA_{ij} + \beta_2 Scort_{ij} + \beta_3 BMI_i + \beta_4 Igender_i + \beta_5 IriskOB_i + \\ & \beta_6 Irace_{AfricanAmerican} i + \beta_7 Irace_{Others} i + \beta_8 Scort_{ij} * GA_{ij} + b_0 i + \epsilon_{ij} \end{aligned} \tag{3}$$

Since we suspected the relationship between EFW and GA may be quadratic in the preliminary descriptive data analysis, a quadratic term of GA was added into the model

$$\begin{aligned} EFW_{ij} =& \beta_0 + \beta_1 GA_{ij} + \beta_2 Scort_{ij} + \beta_3 BMI_i + \beta_4 Igender_i + \beta_5 IriskOB_i + \\ & \beta_6 Irace_{AfricanAmerican} i + \beta_7 Irace_{Others} i + \beta_8 Scort_{ij} * GA_{ij} + \\ & \beta_9 GA_{ij}^2 + + b_0 i + \epsilon_{ij} \end{aligned} \tag{4}$$

We performed a likelihood ratio test between model 3 and model 4.Table 3 shows the result of the test. The result showed there is significant statistical evidence that we add a quadratic term of GA into the model. Therefore, we decided to use model 4 to detect the relationship between EFW and Scort change over the GA

| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|---|---|---|---|---|---|---|---|---|
| modlme | 1 | 13.00 | 7020.89 | 7075.68 | -3497.45 | | | |
| modlme1 | 2 | 14.00 | 6030.58 | 6089.58 | -3001.29 | 1 vs 2 | 992.32 | 0.00 |

Table 3: Likelihood ratio test of model 3 and 4

Table 4: Result of model 4

| | *Dependent variable:* | | |
|---|---|---|---|
| | EFW | | |
| Scort | −26.567 | GA | $-169.982^{***}$ |
| | (68.088) | | (5.130) |
| BMI | −0.056 | Gender | $-21.494^{**}$ |
| | (1.035) | | (10.760) |
| Race2 | −16.114 | Race3 | −4.779 |
| | (13.454) | | (15.568) |
| RiskOB | −9.629 | I(GA^2) | $5.592^{***}$ |
| | (12.277) | | (0.101) |
| Scort:GA | 1.254 | Constant | $1{,}441.410^{***}$ |
| | (2.308) | | (75.030) |
| Observations | 500 | Akaike Inf. Crit. | 6,030.578 |
| Log Likelihood | −3,001.289 | Bayesian Inf. Crit. | 6,089.583 |
| *Note:* | $^{*}$p<0.1; $^{**}$p<0.05; $^{***}$p<0.01 | | |

From the result we know that 1.25 (95% CI:-3.27, 5.77)) grams is expected difference of EFW comparing subjects differing in Scort of 1 ug/mL controlling for other covariates across the course of GA.

We construct a Likelihood ratio test to test whether there is relationship between Scort and EFW change over GA. The null hypothesis is there is no association between EFW and Scort change over the course of GA.($H_0$ $\beta_S crot * GA = 0$) The result of the test statistic is 0.3 with p-value 0.5831(In Appendix). There is no enough statistical evidence to support that there is association between EFW and Scort change over the course of GA in population level.

## 4 Discussion

In our study, we analyze the longitudinal measurements during pregnancy, 500 observations with 9 variables. We first explore the association between the EFW and Scort given all other confounding variables by simple linear model. 1 $\mu$g/dL increased in salivary cortisol is associated with 33.67 (95% CI(-141.44,74.1))grams decreased in the mean of estimated fetal weight with all other variables held constant. We conducted a Wald test analysis to assess the hypothesized that the association between EFW and Scort on the last measurement. The result of the test statistic is -0.62 with p-value 0.54. And it is found that there is no statistically evidence of an association between expected EFW and Scort, focusing on the last measurement.

Moreover, We explore the association between change of the EFW and the change of Scort based on the first and last measurements. We found that the 1 $\mu$g/dL increased in the change of salivary cortisol is associated with 9.38(95% CI(-122.44,141.39)) grams increased in the mean change of estimated fetal weight with all other variables held constant. The result of the Wald test statistic is 0.14 with p-value 0.89. Hence, there is no enough statistically evidence to support an association between the expected change EFW and the change of Scort, focusing on the fist and last measurement.

We quantify the association between EFW and Scort change over the the course of GA using a linear mixed effect model(model 4). And it is found that that 1.25 (95% CI:-3.27, 5.77)) grams is expected difference of EFW comparing subjects differing in Scort of 1 ug/mL controlling for other covariates across the course of GA. We conducted the likelihood ratio test to test whether there is association between the EFW and Scort change over the course of GA.The result of the test statistic is 0.3 with p-value 0.58. There is lack of statistical evident to support that the relationship between EFW and Scort would change over the course of GA.

There are some limitations of the analysis. Firstly, the sample size is limited. We only have 100 patients with 500 observations. And we don't know the process of data collecting, we don't know the data set could represent what kind of population.

Additionally, we used salivary cortisol here to measure the stress of the mother, a more comprehensive tool for the assessment of maternal stress is required. The study could have been benefited from more covariates measured throughout the study. Primarily, mother's age[6] and cigarette smoking habit[7] are factors that were not provided in this analysis, but may have beneficial to control for. Mother's age could impact the body's response to stress, or biologically the estimated fetal weight, and should be considered as a confounding variable within the study. Mother's cigarette smoking habit could also play a role in the estimated fetal weight and would have been an interesting confounding variable to control for. Overall though, the study was able to address the primary question of interest and further studies that investigate this relationship should consider the factor mentioned.

# 5 Reference

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# 6 Appendix

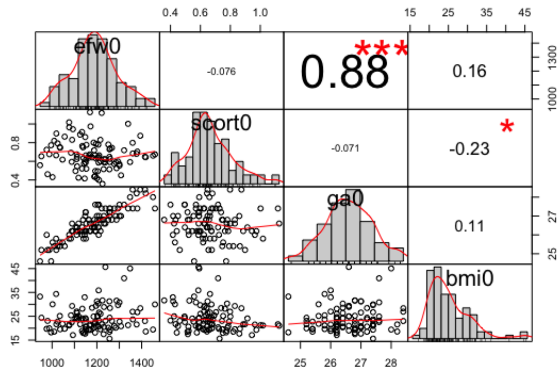


Figure 5: Correlation among continous variables

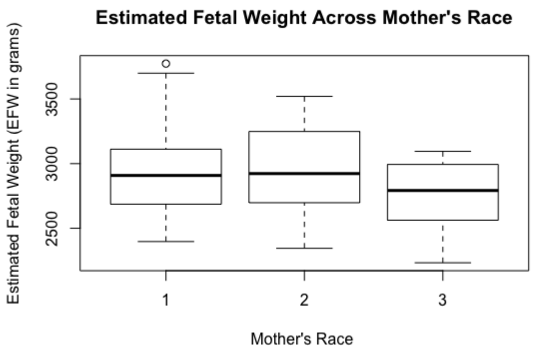


Figure 6: EFW and RACE

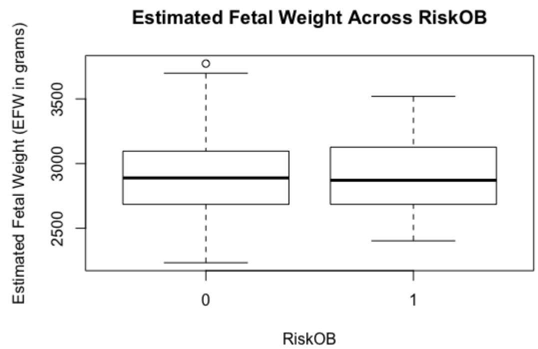


Figure 7: EFW and Risk

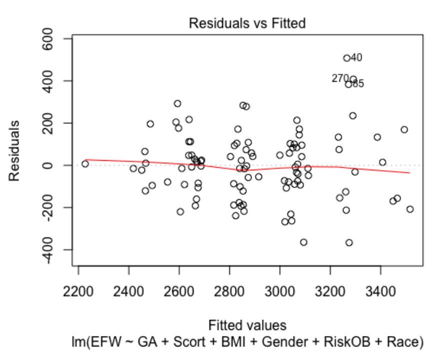


Figure 8: Residuals vs Fitted

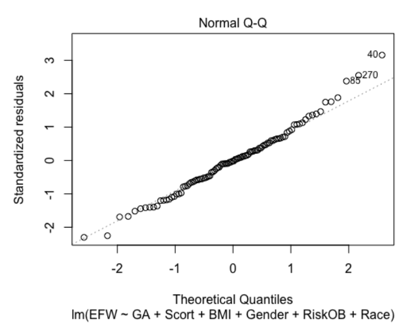


Figure 9: Normal Q-Q

| | Model | df | AIC | BIC | logLik | Test | L.Ratio | p-value |
|---|---|---|---|---|---|---|---|---|
| modlme2 | 1 | 13.00 | 6028.88 | 6083.67 | -3001.44 | | | |
| modlme1 | 2 | 14.00 | 6030.58 | 6089.58 | -3001.29 | 1 vs 2 | 0.30 | 0.58 |

Table 5: Result of Likelihood ratio test of interaction